PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJW/8153-WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/GB2004/001419	International filing date *(day/month/year)* 29.03.2004	Priority date *(day/month/year)* 27.03.2003
International Patent Classification (IPC) or national classification and IPC A61L27/56, A61L27/54, A61L27/36		
Applicant REGEN TEC LTD		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.10.2004	25.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Menidjel, R Telephone No. +31 70 340-3680

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001419

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-17	as originally filed
Claims, Numbers	
1-33	received on 02.02.2005 with letter of 27.01.2005
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001419

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 - The following documents (D1,D2,D3) are referred to in this communication (Article 33(6) PCT); the numbering will be adhered to in the rest of the procedure:
D1: US-A-5 502 092 (SUSZKO PAUL R ET AL) 26 March 1996 (1996-03-26)
D2: WO 99/25391 A (BONETEC CORP) 27 May 1999 (1999-05-27)
D3: US-A-4 997 443 (WALTHALL BENNIE J ET AL) 5 March 1991 (1991-03-05)

- The amendments filed by the applicant do not introduce subject-matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).

2. Novelty (Article 33(2) PCT)

- The subject-matter of present claims 1-33 appears to be novel over the cited prior art for the following reasons (Article 33(2) PCT):
- Documents D1 describes a process for the production of a biocompatible porous matrix of bioabsorbable materials comprising a bioabsorbable polymer, dissolving the bioabsorbable polymer in a volumetric orientation aid to yield a molten solution, solidifying the molten solution to yield an orientation matrix comprising a first and second phase and removing the volumetric orientation aid (second phase) while the solution is solid (Cf. D1, column 4, line 45-column 5, line 33; column 6, lines 2-48; column 7, lines 8-65; column 8, lines 38-64; examples 1-6).

- Document D2, cited by the applicant, describes a biodegradable polymer scaffold comprising an interconnected macroporous network (Cf. D2, page 2, line 20-page 3, line 22; page 9, line 21-page 10, line 29; page 12, line 11-page 13, line 22; page 15, lines 3-28).

- Document D3 describes a transplantable artificial tissue matrix structure containing viable cells made by polymerizing precursors in an aqueous solution to form a shape retaining solid matrix. The reversible gel polymer is dissolved and removed to yield an insoluble, porous matrix containing viable cells (Cf. D3, column 3, lines 16-53; column 3, line 63-column 4, line 29; column 4, lines 40-60; claims 1-18).

None of the cited documents D1 to D3 refers to a tissue scaffold as described in present claim

1 which comprises a matrix comprising a second phase.

3. Inventive Step (Article 33(1),(3) PCT)

- Although novel, the subject-matter of present claims 1-33 cannot be considered as being inventive for the following reasons (Article 33(1),(3) PCT):

- The subjective problem to be solved by the present application is to provide a porous matrix which have good diffusion properties and efficient cells seeding.

- The solution proposed in the present application is a tissue scaffold comprising a matrix as described in present claim 1.

- Document D1, which is considered as the closest prior art, describes a process for the production of a biocompatible porous matrix of bioabsorbable materials comprising a bioabsorbable polymer (first phase), dissolving the bioabsorbable polymer in a volumetric orientation aid to yield a molten solution (second phase), solidifying the molten solution to yield an orientation matrix comprising a first and second phase and removing the volumetric orientation aid (second phase) while the solution is solid.

- The difference between the claimed subject-matter and the teaching of the closest prior art appears to be the presence of a second phase contained within and distributed through the first phase.

- The technical effect of this difference as the surprising technical effect linked to this difference is not clearly mentioned within the application as filed. Therefore, it appears that the feature of present claims 1-33 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

Thus, the subject-matter of present claims 1-33 does not involve an inventive step (Article 33(1),(3) PCT).

4. Industrial Application (Article 33(4) PCT)

- The subject-matter of present claims 1-33 is considered to be industrially applicable; claims

1-33 therefore, satisfy the criterion set forth in Article 33(4) PCT.

CLAIMS

1. A tissue scaffold which comprises a matrix comprising a solid or semi solid first phase and, contained within and distributed through the first phase, a second phase which optionally additionally contains cells, and wherein the matrix has a porous structure.

2. A tissue scaffold according to claim 1, wherein the second phase is solid.

3. A tissue scaffold according to claim 2, wherein the second phase comprises a solid particulate material contained within and distributed through the first phase.

4. A tissue scaffold according to claim 3, wherein the solid particulate material is porous.

5. A tissue scaffold according to any one of claims 1 to 4, wherein the first phase or the second phase or both the first phase and the second phase comprises one or more of the polymers selected from poly(α-hydroxyacids), polylactic or polyglycolic acids, poly-lactide poly-glycolide copolymers, poly-lactide polyethylene glycol (PEG) copolymers, polyesters, poly (ε-caprolactone), poly (3-hydroxy-butyrate), poly (s-caproic acid), poly (p-dioxanone), poly (propylene fumarate), poly (ortho esters), polyol/diketene acetals addition polymers, polyanhydrides, poly (sebacic anhydride) (PSA), poly (carboxybiscarboxyphenoxyphenoxyhexane) (PCPP), poly [bis(p-carboxyphenoxy) methane] (PCPM), copolymers of SA, CPP and CPM poly (amino acids), poly (pseudo amino acids), polyphosphazenes, derivatives of poly [(dichloro) phosphazene], poly [(organo) phosphazenes] polymers, polyphosphates, polyethylene glycol polypropylene block copolymers, natural polymers, silk, elastin, chitin, chitosan, fibrin, fibrinogen, polysaccharides (including pectins), alginates, collagen, poly (amino acids), peptides, polypeptides or proteins, co-polymers prepared from the monomers of these polymers, random blends of these polymers or mixtures or combinations thereof.

6. A tissue scaffold according to claim 5, wherein the polymer is biodegradable.

7. A tissue scaffold according to either claim 5 or claim 6, wherein the polymer is crosslinked.

8. A tissue scaffold according to any one of claims 5 to 7, wherein the first phase or the second phase or both the first phase and the second phase comprises a polymer and a plasticizer.

9. A tissue scaffold according to any one of claims 1 to 8, which additionally contains cells.

10. A tissue scaffold according to claim 9, wherein the cells are provided in the second phase.

11. A tissue scaffold according to either claim 9 or claim 10, in which the cells are animal cells.

12. A tissue scaffold according to claim 11, in which the cells are mammalian cells.

13. A tissue scaffold according to claim 11, in which the cells are human cells.

14. A tissue scaffold according to any one of claims 11 to 13, in which the cells are bone, osteoprogenitor cells, cardiovascular cells, endothelial cells, cardiomyocytes, pulmonary or other lung cells, gut or intestinal cells, cartilage, muscle, liver, kidney, skin, or specialised cells such as placental, amnionic, chorionic or foetal cells, stem cells, chondrocytes, or reprogrammed cells from other parts of the body such as adipocytes reprogrammed to become cartilage cells.

15. A tissue scaffold according to any one of claims 1 to 14, in which the matrix further comprises one or more factors useful for the promotion of tissue growth and development.

16. A tissue scaffold according to claim 15, wherein the factors in the matrix comprise epidermal growth factor, platelet derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor, nerve growth factor, hepatocyte growth factor, transforming growth factors and bone morphogenic proteins, cytokines including interferons, interleukins, monocyte chemotactic protein-1 (MCP-1), oestrogen, testosterone, kinases, chemokinases, glucose or other sugars, amino acids, calcification factors, dopamine, amine-rich oligopeptides, such as heparin binding domains found in adhesion proteins such as fibronectin and laminin, other amines tamoxifen, cis-platin, peptides and certain toxoids.

17. A tissue scaffold according to any one of claims 1 to 16, in which the matrix further comprises drugs, hormones, enzymes, antibiotics, nutrients or other therapeutic agents or factors or mixtures thereof in both the first phase and the second phase.

18. A tissue scaffold according to any one of claims 1 to 17, in which each of the first phase and the second phase of the matrix comprises different drugs, hormones, enzymes, antibiotics, nutrients or other therapeutic agents or factors or mixtures thereof.

19. A process for the production of the tissue scaffold of claim 1, which process comprises the steps:-

1. bringing a first phase into a fluid state;
2. introducing a second phase into the first phase;
3. mixing the first phase and the second phase such that the second phase is contained within and distributed through the first phase; and
4. allowing the first phase to solidify to a solid or semi solid state with the second phase contained within and distributed through the first phase to form a matrix, said matrix also having a porous structure.

20. A process according to claim 19, wherein the second phase is a solid particulate material and wherein the first phase, when in the fluid state, is tacky.

21. A process according to either claim 19 or claim 20, wherein the first phase and the second phase are in particulate form and wherein the particles of the first phase, when mixed with the second phase, coat the particulate material of the second phase.

22. A process according to any one of claims 19 to 21, wherein, in step 4, the first phase is caused to solidify to a solid or semi solid state by the change of a single parameter.

23. A process according to claim 22, wherein the change of a single parameter is selected from a change in temperature, a change in pH, the introduction of a crosslinking, setting or gelling agent, the presence/absence of light, ultraviolet or infra-red curing or under anaerobic conditions.

24. A process according to any one of claims 19 to 23, wherein the second phase comprises a porous solid particulate material.

25. A process according to claim 24, wherein the porous solid particulate material has a porosity of from 10 to 97%.

26. A process according to any one of claims 19 to 23, wherein the first phase or the second phase or both the first phase and the second phase comprises a polymer selected from poly(α-hydroxyacids), polylactic or polyglycolic acids, poly-lactide poly-glycolide copolymers, poly-lactide polyethylene glycol (PEG) copolymers, polyesters, poly (ε-caprolactone), poly (3-hydroxy-butyrate), poly (s-caproic acid), poly (p-dioxanone), poly (propylene fumarate), poly (ortho esters), polyol/diketene acetals addition polymers, polyanhydrides, poly (sebacic anhydride) (PSA), poly (carboxybiscarboxyphenoxyphenoxyhexane) (PCPP), poly [bis(p-carboxyphenoxy) methane] (PCPM), copolymers of SA, CPP and CPM poly (amino acids), poly (pseudo amino acids), polyphosphazenes, derivatives of poly [(dichloro) phosphazene], poly [(organo) phosphazenes] polymers, polyphosphates, polyethylene glycol polypropylene block copolymers, natural polymers, silk, elastin, chitin, chitosan, fibrin, fibrinogen, polysaccharides (including pectins), alginates, collagen, poly (amino acids), peptides, polypeptides or proteins, co-polymers prepared from the

monomers of these polymers, random blends of these polymers or mixtures or combinations thereof.

27. A process according to claim 26, wherein the polymer is biodegradable.

28. A process according to either claim 26 or claim 27, wherein the polymer is caused to undergo crosslinking.

29. A process according to any one of claims 19 to 28, wherein a plasticizer is added to the first phase or the second phase or to both the first phase and the second phase.

30. A process according to any one of claims 19 to 29, wherein cells are incorporated into the second phase.

31. A process according to any one of claims 19 to 30, wherein the first phase transforms to a solid or semisolid state at or close to the body temperature of an animal, including human, and wherein, after the mixing step 3., the mixture is introduced into the body of the animal prior to the solidification step 4.

32. A process according to claim 19, wherein the first phase comprises a material which in step 4 forms a gel.

33. A process according to any one of claims 19 to 32, including an additional step of shaping or partially shaping the matrix before insertion into or onto target tissue.